Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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1 Powles T, Albiges L, Bex A, et al. ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma. *Ann Oncol* 2021; **32:** 1511–19.
2 Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015; **373:** 1803–13.
3 McDermott DF, Lee JL, Bjarnason GA, et al. Open-label, single-arm phase II study of pembrolizumab monotherapy as first-line therapy in patients with advanced clear cell renal cell carcinoma. *J Clin Oncol* 2021; **39:** 1020–28.
4 Choueiri TK, Tomczak P, Park SH, et al. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. *N Engl J Med* 2021; **385:** 683–94.
5 Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018; **378:** 1277–90.
6 Motzer RJ, Russo P, Grünwald V, et al. Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial. *Lancet* 2023; published online Feb 9. https://doi.org/10.1016/S0140-6736(22)02574-0.
7 Vasudev NS, Ainsworth G, Brown S, et al. LBA29 nivolumab in combination with alternatively scheduled ipilimumab in first-line treatment of patients with advanced renal cell carcinoma: a randomized phase II trial (PRISM). *Ann Oncol* 2021; **32:** S1304–05.
8 Motzer RJ, McDermott DF, Escudier B, et al. Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma. *Cancer* 2022; **128:** 2085–97.
9 Atkins MB, Jegede OA, Haas NB, et al. Phase II study of nivolumab and salvage nivolumab/ipilimumab in treatment-naive patients with advanced clear cell renal cell carcinoma (HCRN GU16-260-Cohort A). *J Clin Oncol* 2022; **40:** 2913–23.
10 McKay RR, McGregor BA, Xie W, et al. Optimized management of nivolumab and ipilimumab in advanced renal cell carcinoma: a response-based phase II study (OMNIVORE). *J Clin Oncol* 2020; **38:** 4240–48.
11 Grimm MO, Emilio E, Barthélémy P, et al. Efficacy of nivolumab/ipilimumab in patients with initial or late progression with nivolumab: updated analysis of a tailored approach in advanced renal cell carcinoma (TITAN-RCC). *Proc Am Soc Clin Oncol* 2021; **39:** 4576.
12 Rofi E, Del Re M, Arrigoni E, et al. Clinical pharmacology of monoclonal antibodies targeting PD-1 axis in urothelial cancers. *Crit Rev Oncol Hematol* 2020; **154:** 102891.
13 Allaf M, Kim SE, Harshman LC, et al. LBA67 phase III randomized study comparing perioperative nivolumab (nivo) versus observation in patients (pts) with renal cell carcinoma (RCC) undergoing nephrectomy (PROSPER, ECOG-ACRIN EA8143), a National Clinical Trials Network trial. *Ann Oncol* 2022; **33:** S1432–33.
14 Pal SK, Uzzo R, Karam JA, et al. Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial. *Lancet* 2022; **400:** 1103–16.
15 Duan J, Cui L, Zhao X, et al. Use of immunotherapy with programmed cell death 1 *vs* programmed cell death ligand 1 inhibitors in patients with cancer: a systematic review and meta-analysis. *JAMA Oncol* 2020; **6:** 375–84.

COVID-19 infection, reinfection, and the transition to endemicity

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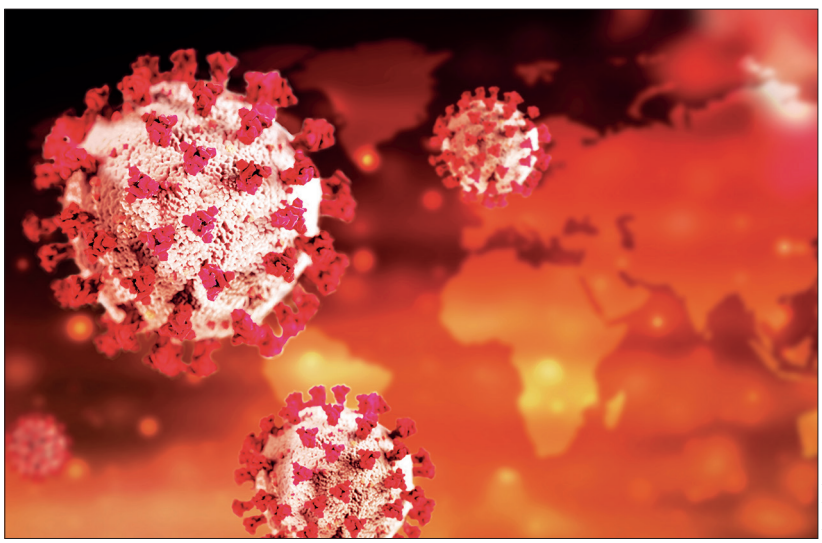
Understanding the protection conferred by previous infection against repeat infection, illness, and severe disease is key to projecting the future epidemiology of COVID-19 and to guiding vaccine policy decisions. In *The Lancet*, The COVID-19 Forecasting Team[1] report data from a systematic review and meta-analysis of 65 studies from 19 different countries estimating the reduction in COVID-19 risk among individuals with previous SARS-CoV-2 infection, compared with those without a previous infection. Although there have been several previous systematic reviews that address this question, the current study adds substantial new information through the inclusion of an analysis of the change in protection conferred by previous infection with time since infection and an analysis stratified by SARS-CoV-2 variant. This analysis is particularly important following the emergence of the omicron variant in late 2021, with rapid spread globally. Currently, in most parts of the world, COVID-19 is dominated by different omicron sublineages, with ongoing emergence of new sublineages demonstrating the importance of potential immune escape.[2]

The COVID-19 Forecasting Team[1] found a high level of protection against reinfection and symptomatic disease for ancestral, alpha, beta, and delta variants (mean pooled estimate >82%) but substantially lower protection (approximately 45%) for the omicron BA.1 variant. Protection against severe disease was high for all variants evaluated (>85% at 40 weeks). Protection against reinfection with alpha, beta, and delta variants waned over time but remained higher than 75% at 40 weeks. By contrast, protection against reinfection by omicron BA.1 waned more rapidly, decreasing to 36% at 40 weeks. The data available for the omicron sublineages BA.2, BA.4, and BA.5, although limited, suggested that protection against these sublineages was lower if the past infection was with a pre-omicron variant compared with omicron; however, reinfection of those with a past omicron infection was higher for BA.4 and BA.5, highlighting the ongoing importance of immune evasion as a selective pressure driving the emergence of new subvariants.

The key limitations of this study include the small number of studies done in low-income and middle-income countries, many of which have had high rates of SARS-CoV-2 infection, and the scarce data available on omicron BA.4 and BA.5 and other emerging sublineages. In addition, studies are needed with longer-term follow-up for the effects of waning protection and the protection conferred by repeated infections with different variants.

The immune escape properties of omicron BA.1 were first detected by routine monitoring of population-level reinfection trends on the basis of epidemiological data.[3] Although molecular surveillance and immunological analyses are essential for understanding the mechanisms underpinning immune evasion,[4] the public health implications of viral evolution are fundamentally an epidemiological question. In the context of high population-level immunity, novel approaches are needed for sustained surveillance to assess the epidemiological consequences of new SARS-CoV-2 variants and sub-lineages, as well as mechanisms to support these platforms and ensure representation of low-income and middle-income countries. Potential approaches could include systematic repeated community testing, such as the innovative Office for National Statistics study in the UK,[5] repeated analyses of routinely collected large datasets,[6] and longitudinal cohort studies.[7] Routine monitoring for changes in epidemiological trends, such as disease severity and repeated infection with different variants in populations with well characterised immune histories, will be essential to maintain alongside platforms for ongoing molecular characterisation of the evolving virus.

Although it is impossible to predict the long-term trajectory of SARS-CoV-2 circulation with certainty, the short duration of immunity combined with high transmissibility of the omicron variant and its sublineages hint that SARS-CoV-2 may not experience the kind of dynamic resonance that drives annual influenza epidemics.[8] Although seasonal factors are likely to drive some variation in SARS-CoV-2 incidence throughout the year, the ratio of the peak incidence to the trough could be much closer to 1. Furthermore, in the long run, most infections will occur in people with strong protection against severe disease because of previous infection, vaccination, or both. Together, these results suggests that, similar to other human coronaviruses, there might be a low seasonal hospitalisation burden associated with SARS-CoV-2.



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The high and sustained levels of protection conferred by previous infection against severe disease have important implications for COVID-19 vaccine policy. By September, 2021, global SARS-CoV-2 seroprevalence was estimated at 59%, with substantial variation in the proportion of immunity induced by infection or vaccination in different settings.[9] Seroprevalence in Africa was estimated at 87% in December, 2021, largely as a result of infection.[9] High levels of immunity are an important contributor to the lower levels of severity observed with infection caused by emerging omicron subvariants.[10] As SARS-CoV-2 epidemiology shifts to more stable circulation patterns in the context of high levels of immunity, studies of the burden and cost of SARS-CoV-2 infection and risk groups for severe disease are needed to guide rational vaccination policy and decisions around prioritisation in relation to other vaccine-preventable diseases.

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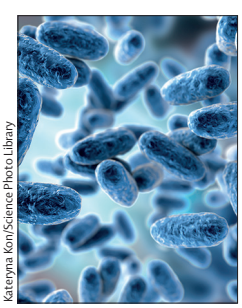
1 COVID-19 Forecasting Team. Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. *Lancet* 2023; published online Feb 16. https://doi.org/10.1016/S0140-6736(22)02465-5.
2 Subissi L, von Gottberg A, Thukral L, et al. An early warning system for emerging SARS-CoV-2 variants. *Nat Med* 2022; **28:** 1110–15.
3 Pulliam JRC, van Schalkwyk C, Govender N, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa. *Science* 2022; **376:** eabn4947.
4 DeGrace MM, Ghedin E, Frieman MB, et al. Defining the risk of SARS-CoV-2 variants on immune protection. *Nature* 2022; **605:** 640–52.
5 Pouwels KB, House T, Pritchard E, et al. Community prevalence of SARS-CoV-2 in England from April to November, 2020: results from the ONS Coronavirus Infection Survey. *Lancet Public Health* 2021; **6:** e30–38.
6 Chemaitelly H, Ayoub HH, AlM S, et al. Protection from previous natural infection compared with mRNA vaccination against SARS-CoV-2 infection and severe COVID-19 in Qatar: a retrospective cohort study. *Lancet Microbe* 2022; **3:** e944–55.
7 Cohen C, Kleynhans J, von Gottberg A, et al. SARS-CoV-2 incidence, transmission, and reinfection in a rural and an urban setting: results of the PHIRST-C cohort study, South Africa, 2020–21. *Lancet Infect Dis* 2022; **22:** 821–34.
8 Dushoff J, Plotkin JB, Levin SA, Earn DJD. Dynamical resonance can account for seasonality of influenza epidemics. *Proc Natl Acad Sci USA* 2004; **101:** 16915–16.
9 Bergeri I, Whelan MG, Ware H, et al. Global SARS-CoV-2 seroprevalence from January 2020 to April 2022: a systematic review and meta-analysis of standardized population-based studies. *PLoS Med* 2022; **19:** e1004107.
10 Davies M-A, Morden E, Rousseau P, et al. Outcomes of laboratory-confirmed SARS-CoV-2 infection during resurgence driven by Omicron lineages BA.4 and BA.5 compared with previous waves in the Western Cape Province, South Africa. *Int J Infect Dis* 2022; **127:** 63–68.

An alternative route to pertussis protection?



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Around 40 years ago, growing concern in many countries about severe adverse events in infants after receipt of parenteral whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids (DTP) drove the development of more highly purified acellular pertussis vaccines. These diphtheria–tetanus acellular pertussis (DTaP) vaccines, which are also administered parenterally, contain one or more purified pertussis proteins. DTaP provides excellent protection against disease in infants and toddlers and its safety profile is much better than that of DTP.[1] Pertussis transmission and disease seemed to be well controlled for many years after the introduction of DTaP.[1]

However, pertussis resurged in the early 2000s, first in adolescents and then in children aged 7–12 years.[2] Studies in mice[3,4] suggested that acellular and whole-cell pertussis vaccines produce fundamentally different immune priming. In studies[5] in convalescent infant baboons (which can replicate human pertussis infection and disease), animals that were previously infected with live pertussis organisms could not be reinfected upon challenge, whereas those immunised with either DTP or DTaP were protected from disease but could become persistently colonised when challenged with live pertussis organisms. Furthermore, DTaP-primed animals, although protected from symptoms, shed pertussis organisms for longer than those given DTP and transmitted pertussis to naive unimmunised baboons housed nearby.[5]

In view of the limitations of acellular pertussis vaccine, a new approach to immunisation is welcome. BPZE1 is a genetically inactivated strain of *Bordetella pertussis* that is administered intranasally and has been systematically assessed in animal models, including infant baboons.[6] In *The Lancet*, Cheryl Keech and colleagues[7] report the results of a randomised, double-blind, phase 2b study of BPZE1 versus tetanus–diphtheria–acellular pertussis vaccine (Tdap) in 300 healthy adults. Patients were randomly assigned (2:1) to receive either 10^9 colony-forming units of BPZE1 or the Tdap vaccine. 85 days after initial vaccination, all patients underwent attenuated challenge with either BPZE1 (10^9 colony-forming units) or placebo. *B pertussis*-specific antibody responses against pertussis toxin, filamentous haemagglutinin, pertactin, and whole-cell extract from nasal secretions (secretory IgA) and serum (IgG and IgA) were measured. Colonisation after BPZE1 challenge was assessed by nasopharyngeal aspiration and culture.

BPZE1 induced mucosal secretory IgA and serum IgG and IgA responses to pertussis antigens, whereas Tdap induced high serum IgG and IgA responses to these antigens but did not induce a consistent mucosal secretory IgA response. Of the 80 BPZE1 recipients who underwent challenge with 10^9 colony-forming units of BPZE1, 72 (90%) did not become detectably colonised with *B pertussis*, and the eight participants who were colonised had low mean colony counts. By contrast, 28 (70%) of 40 Tdap-vaccinated participants were colonised after challenge with BPZE1, and